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EXAMINER

CANELLA, KAREN A

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/559,013

Applicant(s)

ONO ET AL.

Examiner

Karen A Canella

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 15, 19, 41, 54, 56, 60-62, 64, 66, 76, 122-134 and 137 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) 15, 19, 41, 54, 56, 60-62, 64, 66, 76, 122-134 and 137 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

1. Claims 1, 2, 6, 36, 38, 47, 53, 68, 69, 71, 72, 75, 79, 86, 90, 97, 101, 105, 108, 113, 119, 121, 135 and 136 have been canceled. Claims 15, 19, 41, 54, 56, 60, 62, 64, 66, 76, 127, 132, 133 and 137 have been amended. Claims 15, 19, 41, 54, 56, 60-62, 64, 66, 76, 122-134 and 137 are pending and under consideration.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.
3. Claims 15 (19, 123, 62, 122, 128, 127, 126, 125, 129). Claim 41 (62, 124, 130, 131, 132), claim 76 (137). Claim 15 is drawn to a pharmaceutical preparation comprising as agent which enriches selectively the presence of complexes of an MHC molecule and a cancer associated antigen, wherein the cancer associated antigen is a fragment of a cancer associated antigen precursor encoded by the nucleic acid molecule comprising a nucleic acid molecule selected from the group consisting of (a) nucleic acid molecules which hybridize under stringent conditions to a molecule consisting of a nucleic acid sequence as set forth as SEQ ID NO:23 and which code for the cancer associated antigen precursor, (b) degenerate coding sequences of part (a), and (c) complements of (a) and (b). Claims 19, 62, 122, 123 and 125-129 are dependent on claim 15.
4. The rejection of claims 15, 19, 41, 60, 62, 64, 66, 122-132, 135-137 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. is maintained for reasons of record. The instant claims are drawn to pharmaceutical compositions comprising nucleic acids, vectors and host cells. The specification states on page 12, lines 4-7 that "the invention also involves the use of genes, gene products, fragments thereof...in the preparation of medicaments. A particular medicament is for treating cancer, preferably bladder cancer, colon cancer, lung cancer, breast cancer or hepatoma. Thus the application contemplates the administration of pharmaceutical compositions comprising nucleic acids and host cells in gene therapy for the treatment of cancer."

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The specification is not enabling for said pharmaceutical compositions for the reasons set forth below.

(A) As drawn to gene therapy

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

It is well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) that clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the method of using the instant pharmaceutical compositions and host cells thereof in the administration of antigen presenting cells transfected or infected ex vivo (page 9, line 27 to

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page 10, line 5). Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated. Until progress is made in these areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that current data regarding the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claims.

Applicant has amended the claims to recite "ex vivo" therapy in order to obviate the instant rejections. However, the teachings of Orkin, above, indicate that both ex vivo or in vivo administration of nucleic acids was unpredictable (page 7, under the heading "Gene transfer"). Applicant argues that the cited references do not reflect the state of the art at the time of filing but has provided no reference to refute the examiner or to establish that ex vivo administration of nucleic acids was predictable at the time of filing.

Further, even if the specification were enabling for the delivery of the disclosed nucleic acids, the specification is not enabling for a therapeutic use of the expressed polypeptide for the reasons set forth below.

(B) As drawn to nucleic acids encoding peptides which evoke a efficacious response against cancer

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The prior art teaches that tumor cells are phenotypically less stable than normal cells and can escape the immune response of the host by many mechanisms including deficient antigen processing by tumor cells, production of inhibitory substances such as cytokines, tolerance induction, rapidly growing cells which can overwhelm a slower immune response, failure of the host to respond to an antigen due to immunosuppression, tumor burden, infections or age, deficient antigen presentation with the host and failure of the host effector cells to reach the tumor due to the stromal barrier (Paul, *Fundamental Immunology*, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity" and Table 4). Paul teaches that lymphocytes from tumor bearing patients have frequently been found to be cytotoxic to their own tumor cells in vitro, but that this effect was blocked by the addition of sera from said patients. Paul teaches that the constituent of the sera which caused the blocking of the cytotoxicity was unknown, but that antibodies, antibody-antigen complexes and shed antigen have all been implicated in the blocking phenomenon (Paul page 1167, second paragraph under the heading "Immunological Enhancement and Blocking Factors?"). Paul also notes that in some cases, immune response to a tumor antigen may sometimes stimulate the growth of the tumor cells directly (last line under the heading "Immunological Enhancement and Blocking Factors?", page 1167). With respect to the blocking factor found in serum, Apostolopoulos et al (*Nature Medicine*, 1998, vol. 4, pp. 315-320) teach that endogenous antibodies present at the time of administration of a tumor peptide re-routes the immune response from a cellular response to a humoral response. In preclinical experiments with mice, MUC1 peptides targeted to the mannose receptor produce high levels of CTL and a low level of antibodies. However, in human clinical trials a low level of CTL and a high level of humoral response was observed (page 315, first column, bridging paragraph). Apostolopoulos et al teach that the presence of endogenous antibodies which bind to the MUC1 peptide was responsible for this re-routing of the immune response from cellular to humoral due to the Fc portion of the antibody (page 319, first column, lines 7-10) and that mice are devoid of these antibodies (page 315, second column, lines 9-13). Apostolopoulos et al teach that these findings have implication for other immunotherapy approaches (page 318, lines 4-8, under the heading "Discussion?"). In support of these conclusions Jager et al (*PNAS*, 2000, Vol. 97, pp. 12198-12203) teach that patients who do not have antibodies to the cancer testis antigen, NY-ESO-1, were able to

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generate a specific T-cell response to NY-ESO after intradermal administration, whereas patients having antibodies which reacted with said antigen already had T-cells which reacted with target cells expressing said antigen in vitro and said positive patients did not develop significant CTL in response to the administered NY-ESO antigen. The instant specification teaches that the peptide encoded by the claimed nucleic acids was recognized by allogenic antisera (page 17, lines 23-25). However, for the reasons stated above, the presence of an endogenous antibody to a cancer associated antigen can be deleterious to immunotherapy comprising the administration of said antigen, or the nucleic acid encoding said antigen. These references discussed above serve to demonstrate that the induction of a anti-tumor CTL response after the administration of a tumor peptide is unpredictable.

It is well known in the art that primary tumors in situ are often heterogeneous with respect to MHC presentation (for example, the abstracts of Semino et al (Journal of Biological Regulators and Homeostatic Agents, 1993, Vol. 7, pp. 99-105 and the abstract of Algarra et al International Journal of Clinical and Laboratory Research, 1997, Vol. 27, pp. 95-102), and the effect of the claimed vaccine upon such a heterogeneous tumor has not been demonstrated by the specification. Bodey et al (Anticancer Research, 2000 Jul-Aug, Vol. 20, pp. 2665-2676) teach that the failure of methods of treating cancer comprising the administration of tumor antigens is due to the failure of cancer vaccines to eliminate the most dangerous clones within tumor cells which are so de-differentiated that they no longer express cancer cell specific molecules (abstract).

The art recognizes that T-cells are subject to clonal deletion within the thymus of a host and that this mechanism eliminates T-cells which are reactive with self-antigens. The specification teaches that the polypeptide encoded by SEQ ID NO:23 is a self antigen, rather than a mutated self antigen, as it is expressed on normal tissues as well as cancerous tissues. Lauritzen et al (International Journal of Cancer, 1998, Vol. 78, pp. 216-222) teach that clonal deletions of thymocytes is a major event in T-cell tolerance which could lead to a tumor escape mechanism. In transgenic mice homozygous for HLA-specific CD4 T-cells which are specific for a MOPC315 plasmacytoma, injection of a large number of tumor cells results in apoptosis of immature and mature transgenic CD4+8 and CD4 thymocytes. This negative selection was specific for the transgenic thymocytes that would complement the idiotype of the immunoglobulins of the MOPC315 plasmacytoma, because injection of tumor cells from a

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plasmacytoma which had a different idiotype of immunoglobulins failed to elicit the clonal deletion. Lauritzsen et al teach that injection of purified MOPC315 protein, versus the tumor cells, caused a profound reduction of the specific thymocytes specific to the idiotype of the plasmacytoma. Lauritzsen et al conclude that deletion of tumor specific thymocytes may represent a major escape mechanism in patients with cancers that secrete or shed antigens. In the instant case, the antigens are known self antigens. It would be reasonable to conclude that said normal antigens are presented within the thymus to developing thymocytes and T-cells with high affinity for said antigens are deleted as "self?". It would be also reasonable to conclude that administration of the claimed polypeptides or cells expressing said polypeptides would not result in an efficacious vaccine as a T-cell response would not be evoked due to the process of clonal deletion in the thymus, rendering the host devoid of T-cells which are specific to the self-protein. Sarma et al (Journal of Experimental Medicine, 1999, Vol. 189, pp. 811-820) states that a critical issue in therapeutic regimens comprising the administration of tumor antigens for immunotherapy is whether unmutated tumor antigens which are expressed in normal cells impose special restrictions on the CTL response in vivo. Using transgenic mice wherein the antigen specific T cells specific for the P1A non-mutated tumor antigen are expressed at high levels and remain responsive to the P1A antigen when assayed in vitro, it was found that P1A antigen expressed in the thymus resulted in clonal deletion of said specific T-cells. Sarma et al note that although said transgenic mice produce an overwhelming majority of T cells that are specific for P1A, said mice are no more resistant to cells expressing P1A than non-transgenic litter mates. Sarma et al concludes that even though P1A can be a tumor rejection antigen, the effector function of P1A specific CTL is restrained in vivo and that these results have important implications for the strategy of tumor immunotherapy. With regard to the treatment of cancer as a genus of diseases comprising in particular bladder cancer, colon cancer, lung cancer, breast cancer or hepatoma (page 12, lines 4-7), it cannot be anticipated that a T-cell clone would be available after thymic selection in patients having cancers of all types, wherein said T-cell would react with said antigen in the context of HLA-A24 or any other MHC molecule. It is also recognized in the art that the isolation of CTL from a cancer patient which can lyse target cells in vitro has no apparent nexus with anti-tumor cytolytic activity in vivo. Ohlen et al (Journal of Immunology, 2001, Vol. 166, pp. 2863-2870) teach that T-cells recognizing normal proteins

expressed in tumors can be isolated in vitro, but that the existence of said T-cells does not preclude in vivo anergy induction and deletion (page 2863, second column, lines 1-6 of the last paragraph). Antoinia et al (International Immunology, 1995, Vol. 7, pp. 715-725) teach that T-cells which are impaired in the ability to proliferate in response to antigen and unable to reject tumors in vivo were fully functional as CTL lymphocytes in vivo (page 724, first column, first full paragraph). These references serve to demonstrate that the lysis of target cells expressing DAGE antigen in vitro does not constitute evidence that said T-lymphocytes would be effective at lysing tumor cells in vivo.

It is noted that the broad genus of cancer types (e.g. bladder cancer, colon cancer, lung cancer, breast cancer or hepatoma) to which the specification asserts the claimed pharmaceutical compositions would be useful in treating would not be expected to initiate or maintain the same growth kinetics. It is unclear whether all patients having a cancer expressing the disclosed antigen would have T-cells which were specific from the disclosed antigen, as the art teaches that the presence of a small number of tumor cells or the presence of a large number of tumor cells gives rise to tolerance (Paul, page 1166, second column, lines 19-23 under the heading "Sneaking Through?"). Based on this observation, it is reasonable to conclude that a small number of slow growing tumor cells would elicit tolerance, and a large number of rapidly growing tumor cells would also elicit tolerance in line with the bi-phasic response reported by Paul. Thus, it appears that the interaction of the tumor cells with the host can produce tolerance by means of clonal deletion within the thymus of said host.

It is concluded based on the references discussed above, that the state of the art with respect to treating patients with cancer by means of administering tumor antigen precursors or tumor antigens is unpredictable. The specification does not provide any disclosure that the administration of the claimed pharmaceutical preparations comprising nucleic acids would generate CTLs which lyse the cells of a tumor in situ, and it cannot be predicted that all patients having cancer expressing the polypeptide encoded by SEQ ID NO:23 would all have a T-cell repertoire that would include a T-cell specific for the disclosed self antigen. Without said T-cell in the repertoire of the host, presentation of said antigen by an antigen-presenting cell after vaccination with the disclosed polypeptide or cell expressing said disclosed polypeptide would not evoke a T-cell response, as the appropriate T-cell would not be available in the periphery to

be activated by said antigen-presenting cell. Thus, without a demonstration that the administration of the claimed polypeptides or cells expressing said polypeptides overcomes immunosuppression of the host, the rapid growth of the target tumor cells, failure to access the tumor because of the stromal barrier and tolerance induction in the host and objective evidence that the target tumor cells in vivo present adequate tumor rejection antigen on the surface of all the tumor cells, one of skill in the art would be subject to undue experimentation in order to use the claimed polypeptides or cells expressing said polypeptides as vaccines as all of these factors would need to be tested in vivo.

Further, it is noted that claims 15, 41 and 127 are drawn to nucleic acid which hybridize to SEQ ID NO:23 and which code for cancer associated antigen precursors. Section (c) of said claims specifically recite the limitation "complements" in reference to the above nucleic acids encoding the tumor associated antigen precursor. It is unclear how a pharmaceutical composition comprising a nucleic acid which hybridizes to SEQ ID NO:23 could be used in the instant invention because said anti-sense sequence would not be expected to encode a fragment of the amino acid sequence encoded by SEQ ID NO:23, and therefore would not be expected to associate with an MHC molecule in a manner that is similar to the fragments of SEQ ID NO:23. As such, only said complements would provide the requisite T cell epitopes which are required for an efficacious immune response.

Given the unreliable state of the art with respect to gene therapy in general, and tumor immunotherapy with tumor derived peptides, and given the lack of teachings regarding the coding sequence of anti-sense SEQ ID NO:23 it is concluded that one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the disclosed methods of treatment.

5. Applicant argues that Apostolopoulos et al statement "Our study demonstrates that cross-reactive anti-Gal antibodies are responsible for the switch of the immune response from cellular to humoral in MUC1 targeted immunotherapy, and the finding may be relevant to other immunotherapeutic approaches" is in the context of being doubtful about the nexus to other immunotherapies rather than suggestive. This has been considered but not found persuasive in the context of the entire reference. Apostolopoulos et al present a hypothesis that the presence

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of endogenous antigens cause a bias in the immune response to an administered self-antigen towards a humoral response rather than a cellular response. There is no reason to believe that the general mechanism presented by Apostolopoulous et al would not be applicable to any other self tumor antigen.

Applicant argues that Apostolopoulous et al is able to overcome the problem of antibody-mediated humoral immune response by ex vivo therapy. It is noted that Apostolopoulous et al do not suggest or teach ex vivo gene therapy. Apostolopoulous et al pulse macrophage ex vivo with a specific tumor peptide. Administration of said macrophage to mice harboring said tumor resulted in a CD8 mediated CTL response in the presence of the antibodies which would bind to the tumor peptide. Apostolopoulous et al suggests that these technique could well be a solution for the treatment of humans. This has been considered but not found persuasive. The instant specification does not provide any teachings or guidance on a peptide which cloud be used to pulse macrophage ex vivo which would present the peptide to T-cells, resulting in an activated T-cell that would recognize the same tumor peptide on the surface of the tumor cell. Without prior knowledge as to a specific eptiope being presented in the context of MHC I on the surface of the tumor cells, one of skill in the art would not be able to predict a peptide to use in the macrophage activation.

Applicant argues that Jager et al do not reinforce the teachings of Apostolopoulous et al because Jager et al clearly states that immunotherapy was effective in subjects having a pre-existing antibody response to the protein. This has been considered but not found persuasive. Jager et al states "By using ELISPOT as the primary monitoring assay, there was a clear distinction in the response of the seronegative and seropositive patients to the 11- and 9-mer NY-ESO-1 peptides. In seronegative patients, the 11-mer response predominated during the initial stage of the immunization, with the 9-mer response developing only after repeated peptide vaccinations. The 11-mer response can be rapid and strong...or delayed" Jager et al further state "In contrast with the response of seronegative patients to NY-ESO-1 peptide vaccination, seropositive patients show a prominent 9-mer reactivity both pre- and post-vaccination, whereas the 11-mer response was generally of lower magnitude". It is noted that neither the seronegative nor the seropositive devolved any response against the second 9-mer peptide (p155-163). Jager et al further teach that despite temporary disease stabilization and strong CD8 T-cell and DTH

reactivity to NY-ESO-1, three of five patients developed a metastatic lesion while undergoing the immunotherapy. Jager et al suggest that the metastatic lesion may be due to the emergence of NY-ESO-1 antigen-loss or MHC-loss variants because of the strong selective pressure. It is noted that some patients receiving the vaccines experienced disease progression without prior disease stabilization. Jager et al indicate that said patients undergoing immediate disease progression might be those with a pre-existing spontaneous NY-ESO-1 antibody. Jager et al conclude that said patients would be considered less favorable candidates for NY-ESO-1 vaccination because NY-ESO-1 escape variants may have already been formed. Clearly, it cannot be predicted which patients will experience disease progression and which patients will experience disease stabilization, or which peptides will be effective at eliciting disease stabilization in a given patient.

Applicant argues that the examiner's statement that "an induction of a CTL response is unpredictable" was not relevant because a CTL response is not required by the claims. This has been considered but not found persuasive. The specification teaches only the use of the instant method in immunotherapy. It is accepted in the art that the induction of a CTL response against a tumor is necessary to kill tumor cells. One of skill in the art would not know how to use the claimed method if an induction of a CTL response were not a therapeutic target.

Applicant states that it should not be necessary to provide human clinical trial data to enable the invention. It is noted that the requirement for enabling an invention is related to the unpredictability in the art: for predictable art, the enablement requirement is low. For instant methods drawn to detecting cancer by means of nucleotide hybridization. In other arts, such as immunotherapy, the unpredictability in the art is high. Clearly immunotherapy is not administered on a routine basis, but is performed, as acknowledged by applicant, in experimental clinical trials. Thus the enablement requirement is high.

Applicant argues against the examiner reasoning that T-cells which recognize foreign antigens are subject to clonal deletion in the thymus. Applicant contends that because the protein is expressed in testis which is an immune privileged site, clonal deletion would not be expected to occur. This has been considered but not found persuasive. The mechanisms governing the modulation of the immune response in immune privileged sites are not well known in the art. Applicant has not provided any publication to teach an alternative mechanism of immune

modulation at immune privileged sites which discounts clonal deletion in the thymus. further, it is noted that NY-ESO-1 is also a cancer-testis antigen, and one of skill in the art would not be able to predict which peptide would induce an immune response in a patient that would lead to disease stabilization or regression rather than the direct disease progression as was observed in some cases.

Applicant argues that the findings in Antoinia et al that CTLs recognizing the DAGE antigen or at least one peptide thereof do not effectively lyse tumor cells and that this has not bearing on the instant methods. Applicant further argues that the Jager et al reference would interpret the results of Antoinia et al to mean that the results cannot be broadly interpreted over all tumor antigens. This has been considered but not found persuasive. Interpreting the results of Antoinia et al in light of the results of Jager et al further reinforces the unpredictability of the immunotherapy art. As applied to the instant invention, one of skill in the art would not be able to predict if the instant invention would results in CTLs recognizing the instant antigen for the same reasons that it could not be predicted that the second NY-ESO 9-mre peptide did not elicit any DTH response in any patient and which the CTL recognizing the DAGE antigen do not effectively lyse tumor cells. .

Applicant argues against the examiners assertion that part of the escape from immune recognition is either very slow growth of large numbers of tumor cells or very fast growth of small numbers of tumor cells would be able to escape recognition. The applicant is taking the examiners statement out of context. The art teaches that growth kinetics plays an important role in tolerance induction and is well known in the art as evidence by publication in an immunology text book (Paul, page 1166, second column).

Applicant argues that it is not proper to reject claims for lack of enablement because there may be some inoperative embodiments encompassed within the scope of the claim. Applicant is relying on overcoming the immune response anergy by administering the tumor protein to a cell which expresses MHC. This has been considered but not found persuasive. It is well know in the art that T-cells need two signals to become activated. The first is the recognition of the immunogenic eptiope in the context of MHC by the T-cell receptor. The second is the engagement of the CD28 receptor on the T-cell by a ligand or molecule which activates said CD28 receptor (abstract of King et al, European Journal of Immunology, 1995,

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vol. 25, pp. 587-595). Without this second signal, the T-cell will be anergic rather than activated. The instant invention does not overcome this problem of supplying the second signal in vivo. There is no objective evidence that a single operative embodiment is encompassed by the scope of the claims because of the unreliability of the art.

Applicant argues that it is not reasonable to assume that a person would lack a T-cell receptor complementary to the tumor cell antigen of the instant invention expressed in the MHC. This has been considered but not found persuasive. It is well known in the art that humans are heterogeneous for T-cell receptors in the same way that they are heterogeneous for B cells. It is not unreasonable to assume that some individuals would mount a weak response to smallpox and other individuals would mount a robust response depending on their particular MHC genes. Further, infectious disease antigens have the ability to activate the immune system via receptors that are not available for tumor peptide, such as the toll-receptor, wherein said activation is independent of MHC (Medzhitov et al, Science, 2002, Vol. 296, pp. 298-300, under the heading "Recognition of Microbial Nonself").

Applicant argues that the claims are not directed to the prevention of cancer, but the reduction in occurrence and the slowing of growth of said cancers. This interpretation is no different from the examiners interpretation of the instant invention, which for the reasons set forth above, lack enablement. Applicant argues that the examiners rejection was based on mere possibilities of difficulties that are based on examples selected from the literature and these difficulties are necessarily applicable to an immunological approach to the treatment of cancers expressing OY-TES-1. First, a large amount of the rejection was taken from an immunology text (Paul) and not selected from the literature. This represents what is well known in the art and not a collection put together by the examiner for the purpose of rejecting the instant claims. Second, it is noted that as of the instant action, immunotherapy of tumors by means of administering antigens present on said tumors is at best an experimental procedure. Thus, the state of the art at the time the instant application was filed was unreliable.

6. The rejection of claim 54 under 35 U.S.C. 102(b) as being anticipated by The New England Biolabs Catalog (1993-1994, page 91) is maintained for reason of record. Claim 54 is drawn in part to a complement of a nucleic acid molecule which hybridizes to SEQ ID NO:23

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under stringent conditions and which codes for a cancer associated antigen precursor. The New England Biolabs Catalog discloses Random Primers on page 91 which would be a complement of a nucleic acid which would hybridize to SEQ ID NO:23.

Applicant maintains that the random hexamers cannot anticipated the instant claims because they do not code for a cancer antigen precursor. this has been considered but not found persuasive because section (c) of claim 54 does not require that the complement encode a cancer associated antigen precursor.

7. All other rejections and objections as set forth in the previous Office action are withdrawn.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

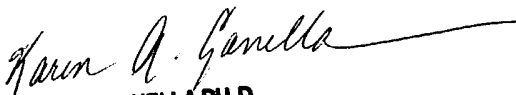
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571)272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.

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KAREN A. CANELLA PH.D
PRIMARY EXAMINER